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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.:	09/583,228
Filing Date:	May 26, 2000
Applicant:	Seth
Group Art Unit:	1615
Examiner:	M. Bahar
Title:	SUSTAINED RELEASE VERAPAMIL PHARMACEUTICAL COMPOSITION FREE OF FOOD EFFECT AND A METHOD FOR ALLEVIATING FOOD EFFECT IN DRUG RELEASE
Attorney Docket:	8674-000004

Commissioner of Patents and Trademarks
Washington, D.C. 20231

Declaration Under 37 C.F.R. § 1.132 of Dr. Pawan Seth

I, Pawan Seth, declare as follows.

1. I hold a PhD in Pharmaceutical Technology – 1986 – from University Louis Pasteur, Strasbourg (France). I subsequently worked as Director of Research and Development, Quality Assurance in Mepha (Basel, Switzerland) until 1994. I am skilled in the development of
   - Controlled release products in multiparticulate units and single oral units.
   - Delayed release products.
   - Therapeutical Transdermal Systems.
   - Colon Delivery products.
   - Bioavailability enhancement.
   - Semi solid topical products

2. I am the co-founder of PharmaPass LLC, the present assignee, where PharmaPass is specialized in designing new galenic formulations for various drugs.

3. I am named as an inventor in 17 granted US patents. I am an inventor of the instant invention.

4. I have read and understood the Morella reference cited in the course of the examination of the instant invention. I have carried out tests to show the superior results of the composition presently claimed versus the Morella formulation.

5. Tablet compositions were manufactured according to the following table.

Verapamil HCl	240.00				
Methocel Pr K100LV CR	15.00				
Methocel Pr K15M CR	40.00				
Avicel PH 101	25.00				
Plasdone K29/32	20.00				
Aerosil 200	1.50				
Magnesium Stearate	3.50				
Isopropyl Alcohol 99% USP	42.00				
PEG 1450		1.44	12		
Dye Blend Yellow DB1770		0.11	1		
Eudragit L 30 D-55		7.03	58		
Syloid 244 FP		2.80	23		
Triethyl Citrate		0.72	6		
Purified Water		80.00			
PEG 1450				2.14	18
Diethyl Phthalate, USP/NF				0.86	7
Ethocel 10 STD Premium				4.09	34
Eudragit L 100				0.91	8
Talc (Lo Micron)				4.00	33
Ethyl Alcohol 200 Proof				114.00	

Column 2 shows the ingredients of the core. The core is manufactured according to the instant patent application. Column 3 shows the ingredients of a coating according to the current invention. This coating is manufactured and deposited on the core according to the instant patent application. Column 5 shows the ingredients of a coating according to the Morella patent. Eudragit L100 is a 1:1 methacrylic acid: acrylic acid ethyl ester copolymer. The Morella coating corresponds to formulation 3 of column 14 of the Morella patent, with the amounts in Morella being divided by approximately 22 to arrive at the ingredient levels in the Table. The Morella-type coating is manufactured and deposited according to the Morella patent. Columns 2 and 4 give the corresponding percentages by weight of the individual ingredients in the coatings.

6. The in vitro dissolution profiles have been determined using the method disclosed in the Morella patent (USP Buffer pH 7.5 and pH (0.1 NHCl), basket 50 rpm).

7. Annex 1 gives the results at pH 1.2. At this pH value, both polymers of the coatings are insoluble; hence the respective dissolution profiles of the coatings are similar.

8. Annex 2 gives the results at pH 7.5. In this case, the dissolution profile of the composition of the invention is similar to the prolfile of the core, while the dissolution profile of the Morella composition is quite different. In this case, the polymer used in the invention is soluble, while the one of Morella is not. Note that the Morella patent shows a profile similar in both conditions.

9. These results show that the compositions of Morella and of the invention are different and will exhibit different behavior in the gastrointestinal (GI) tract. In the acidic medium of the stomach, both compositions will behave similarly. But the Morella composition will not substantially dissolve in the intestines (where pH is higher, typically above 5.5) while the composition of the invention will. This will provide distinct effects.

10. The coated formulation of the invention has different profiles at different pH. At pH 1.2, the formulation of the invention does not start to release the drug till about 4 hours, while at pH 7.5 the drug starts to release after 30 minutes. In order to avoid the food effect and still get very effective amount absorbed, the drug needs to be released in the intestine, which is achieved by the formulation of the invention. In contrast, the Morella formulation simply slows the release of the drug throughout the GI tract. It shows no difference in the release of the drug in the stomach or the intestine.

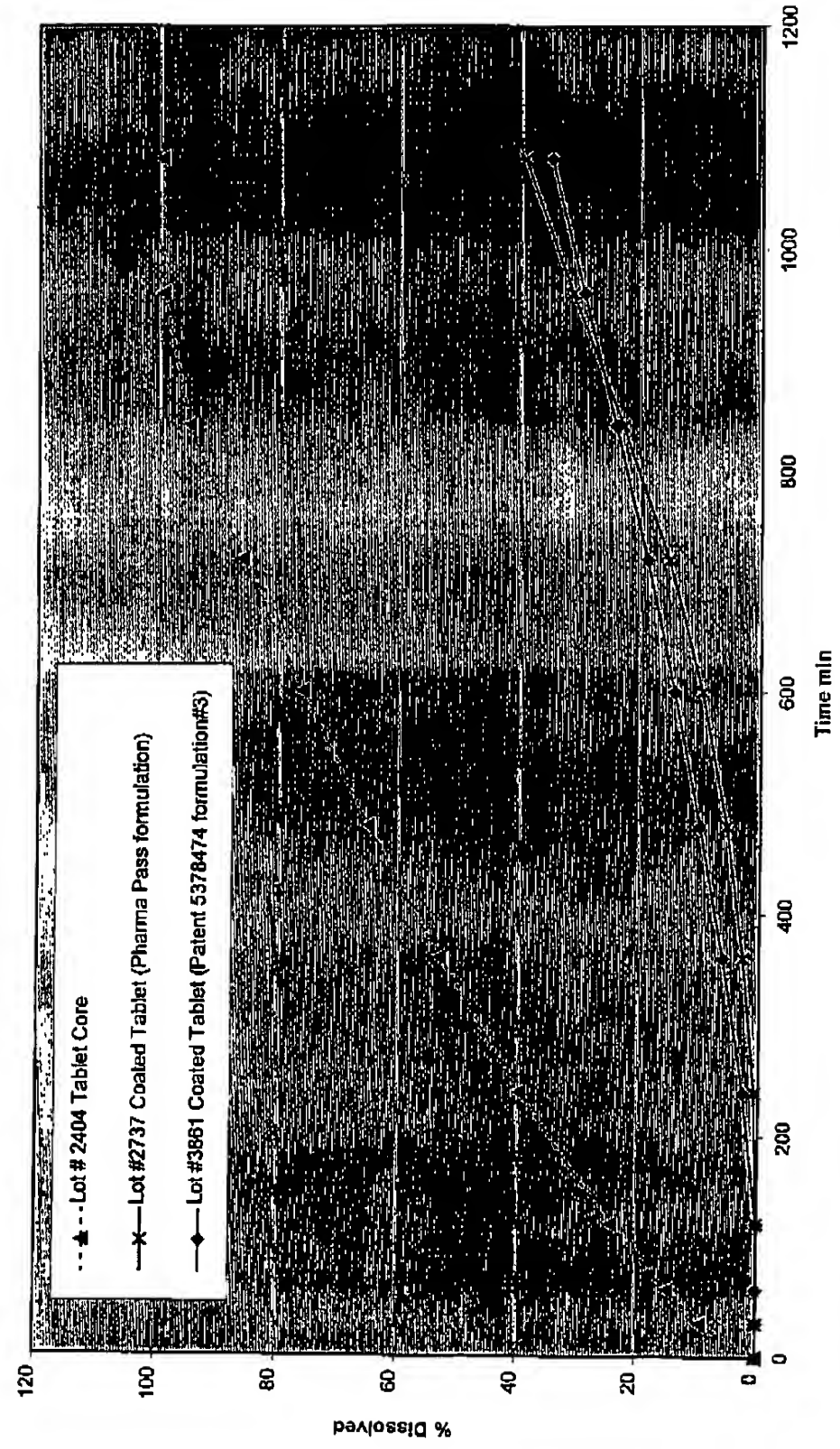
11. The release profile from the Morella formulation indicates that very little drug will be absorbed in the body. Since the drug released in the body is only about 20% after 18 hours, it actually does not avoid the food effect, but the difference in the fed and non fed conditions can not be detected. For example, if there is 30% food effect (difference between fed and fasting absorption), 30% of 20% = 6 % of the total is insignificant, but this is not because of avoiding the food effect – it is because of the poor drug absorption.

12. All statements made herein of my own knowledge are true. All statements made herein on information and belief are believed to be true. These statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonable, or both, under 18 U.S.C. 1001, and may jeopardize the validity of the application or any patent issuing thereon.

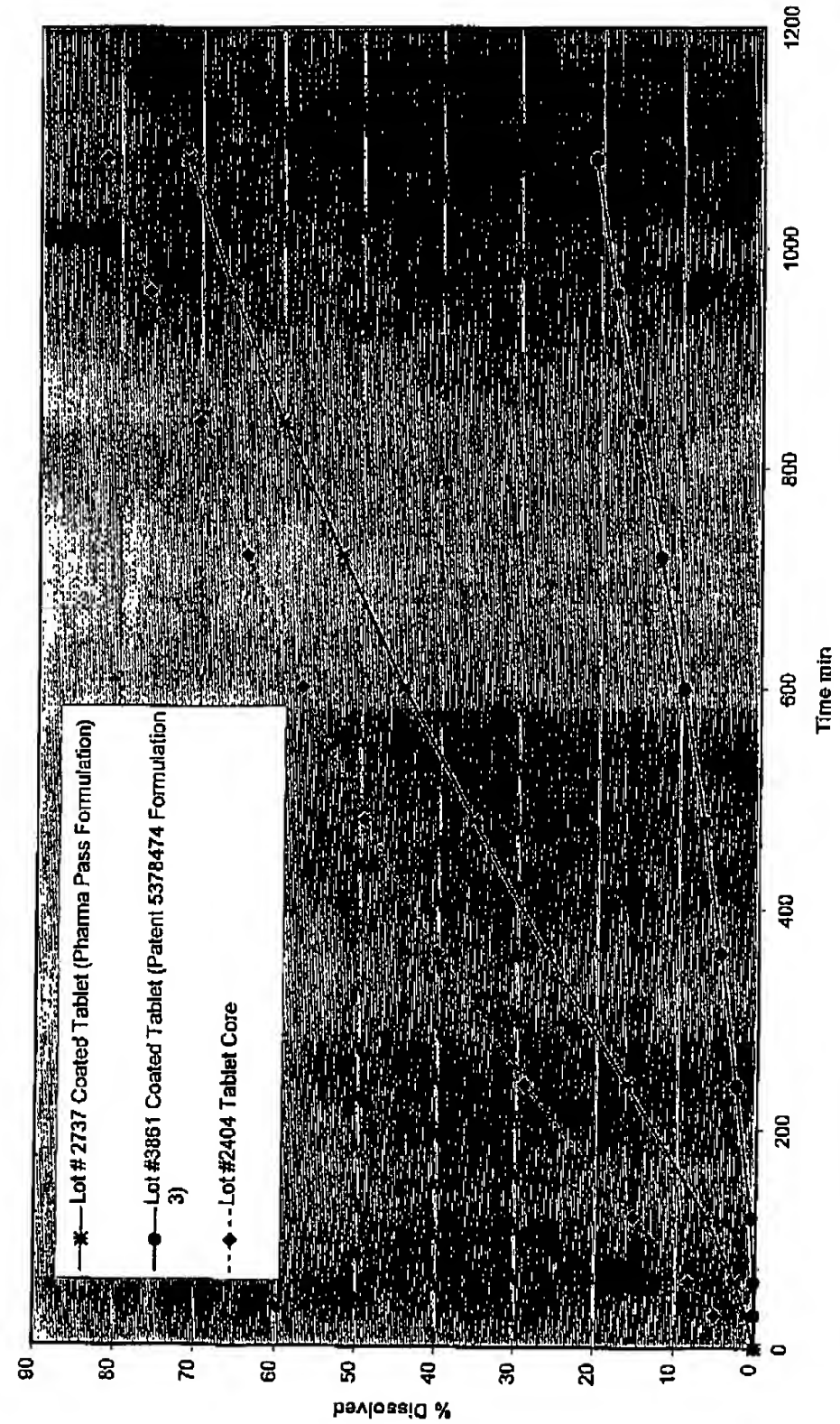
4, Oct. 2002
Date

Pawan Seth
Pawan Seth

Annex 1



Annex 2



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FROM: Mark A. Frentrup MAF

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COMMENTS:

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Mark A. Frentrup